IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	)	C.A. No. 23-975-RGA-SRF

DEFENDANT'S POST-TRIAL RESPONSIVE BRIEF REGARDING NON-INFRINGEMENT OF U.S. PATENT NO. 11,826,327

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Dated: July 24, 2025

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES
(continued)

Page(s)

Other Authorities

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF ABBREVIATIONS

Asserted Patents & Parties

'327 Patent	U.S. Patent No. 11,826,327
Asserted claims of the '327 patent	Claims 1, 5, 6, 9, 14, 17
UTC/Plaintiff	United Therapeutics Corporation
Liquidia/Defendant	Liquidia Technologies, Inc.

Commonly Used Terms & Abbreviations

6MWD	Six-minute walk distance
Dr. Channick	Richard Channick, M.D.
Dr. Nathan	Steven Nathan, M.D.
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
FOF	Liquidia's Findings of Fact
ILD	Interstitial Lung Disease
INCREASE	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects With Pulmonary Hypertension Due to Parenchymal Lung Disease
iTRE	Inhaled treprostinil
Lancet Publication	S. Nathan, et al., *Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study*, The Lancet Respir. Med, (2021), published online June 29, 2021 https://doi.org/10.1016/S2213-2600(21)00165-X (DTX9)
Liquidia Open. Br.	Liquidia's Post-Trial Opening Brief Regarding Invalidity of U.S. Patent No. 11,826,327 (D.I. 424)
PAH	Pulmonary arterial hypertension (Group 1 PH)
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease (Group 3 PH)
PK	Pharmacokinetics
POSA	Person of ordinary skill in the art
NDA	New Drug Application
NEJM Paper	A. Waxman, et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N. Eng. J. Med. 384(4):325 (2021) (DTX363)
NT-proBNP	N-terminal pro b-type natriuretic peptide
UTC Br.	UTC's Opening Post-Trial Brief Regarding Infringement (D.I. 426)
UTCFOF	UTC's Proposed Findings of Fact Related to Infringement (D.I. 427)

I. INTRODUCTION

Yutrepia is not a generic of Tyvaso and is not considered an equivalent product, thus UTC's reliance on INCREASE does not establish infringement. Further, method claims 5, 6, 9, and 17 require measuring the claimed outcomes to determine if they have been infringed. But Yutrepia is not approved for those outcomes, they are not on the label, measuring them is not required, and Liquidia provides no instructions to measure the outcomes when administering Yutrepia. There is no direct or induced infringement of claims 5, 6, 9 and 17.

II. FACTUAL BACKGROUND

Please see Defendant's accompanying findings of fact.

III. YUTREPIA DOES NOT INFRINGE CLAIMS 5, 6, 9 AND 17

A. Yutrepia Is Not Equivalent to Tyvaso

Yutrepia is not approved for any of the uses and outcomes in claims 5, 6, 9 and 17, and the label nowhere mentions NT-proBNP, exacerbations of ILD, FVC, or measuring 6MWD. FOF178-185. Thus, UTC treats Yutrepia like a generic and asserts, based on INCREASE, that Liquidia told the FDA and doctors that Yutrepia "will perform equivalently to Tyvaso in PH-ILD." *See, e.g.*, UTCFOF11; UTC Br., 1, 3. Not so. Because Liquidia followed the 505(b)(2) NDA pathway, and because Yutrepia has an entirely different formulation administered with a completely different inhalation device than Tyvaso, it is not a generic product. FOF172-174. Yutrepia is also not "pharmaceutically equivalent" or "therapeutically equivalent" to Tyvaso and is not an AB rated generic. FOF174; *Amarin Pharms., Inc. v. Hikma Pharma USA Inc.*, 104 F.4th 1370, 1374 (Fed. Cir. 2024) (discussing AB rating and therapeutic equivalence). Accordingly, FDA regulations prevent Liquidia from making any claim, explicitly or implicitly, that Yutrepia will perform equivalently to Tyvaso in PH-ILD patients. FOF174, 178; 21 CFR §§ 202.1(e)(6)(i)-(ii), 201.57(c)(2)(iv). And any inference UTC seeks to draw regarding "equivalency" to Tyvaso runs

contrary to §6.1 of the Yutrepia label, warning doctors against extrapolating clinical trial results of one drug to outcomes in clinical practice of a different drug. FOF185; *Otsuka Pharm. Co. v. Torrent Pharms. Ltd., Inc.*, 99 F. Supp. 3d 461, 490 (D.N.J. 2015) ("[A] warning is just that—a warning."). Dr. Nathan also admitted that data, other than INCREASE, would be needed to prove infringement if a different version of iTRE were evaluated. FOF177. Yutrepia ***is*** an admittedly different version of iTRE than Tyvaso, and UTC provided no other data than INCREASE. *Id.*

The only "equivalency" UTC can actually point to is with respect to *dosing*, not performance. UTCFOF9, 14; PTX291, 15. That dosing information, however, reflects only that the compared doses will yield comparable systemic exposures based on a PK study conducted in healthy volunteers that cannot support an efficacy claim—a point Dr. Nathan did not rebut. FOF175, 189-190. Systemic drug levels do not reflect efficacy of a locally-acting inhaled drug like Yutrepia. FOF189. Thus, UTC is wrong that "comparable pharmacokinetics" indicate equivalent efficacy, and thus infringement. *See Belcher Pharms., LLC v. Hospira, Inc.*, 450 F. Supp. 3d 512, 540 (D. Del. 2020), *aff'd*, 11 F.4th 1345 (Fed. Cir. 2021) ("One does not prove infringement by pointing to . . . bioequivalency, between two products[.]"); *Abbott Lab'ys v. Sandoz Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009) (if "bioequivalency meant per se infringement, no alternative to a patented medicine could ever be offered to the public during the life of a patent.") (citation omitted).

B. Doctors Will Not Directly Infringe Because the Claims Require Measurements

Direct infringement fails because doctors would not measure the numerical or statistically significant outcomes required by method claims 5, 6, 9 and 17, which must be measured before and after administration. FOF180-184. For claims 6 and 9, a doctor would need to treat multiple patients, measure exacerbations of ILD and/or FVC, aggregate the data and perform a statistical analysis, which is not normally done in clinical practice. FOF183. If measurements are not taken,

doctors would not know whether the claimed outcome was met. FOF180-184. The experts agree that the Yutrepia label neither mentions these claimed results nor suggests measuring them to safely and effectively use Yutrepia; therefore, no doctor will directly infringe any of these claims. FOF180-185. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014) (A method claim "is not infringed unless all the steps are carried out."); *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1380 (Fed. Cir. 2022) (finding noninfringement because the drug, prescribed in practice, did not meet all claim elements).

Further, because Yutrepia is not approved for any dependent claim outcomes, and the label does not even mention them, infringement under §271(e)(2) cannot be found for claims 5, 6, 9 and 17 and a §271(e)(4) injunction cannot be granted with respect to those claims. *See,* D.I. 426, 9 (asserting infringement and relief only under §§ 271(e)(2) and 271(e)(4))[1]; FOF178; *H. Lundbeck A/S v. Lupin Ltd.*, 87 F.4th 1361, 1368-69 (Fed. Cir. 2023) ("Our cases establish that 'the use ... claimed in a patent' under section 271(e)(2)(A) must be the use for which an applicant is seeking marketing approval."); *see also Warner-Lambert Co. v. Apotex Corp.,* 316 F.3d 1348, 1359 (Fed. Cir. 2003); *Allergan, Inc. v. Alcon Lab'ys, Inc.*, 324 F.3d 1322, 1322-23 (Fed. Cir. 2003); *Bayer Schering Pharms. v. Lupin Ltd.*, 676 F.3d 1316, 1320-21 (Fed. Cir. 2012).

If the Court instead considers infringement of claims 5, 6, 9, and 17 under §271(b), which UTC abandoned, it also fails. *See.* UTC Br., 9. UTC argues, based on INCREASE, the claimed outcomes would likely result from prescribing Yutrepia. UTCFOF18-21; UTC Br., 4-8. But Dr. Nathan admitted this away, testifying that he would be "entirely speculating" as to whether Yutrepia would produce the same results from INCREASE. FOF136, 177. Speculating as to the

[1] UTC abandoned its claims for infringement and relief under §§ 271(a)-(c) and §283 set forth in its Amended Complaint (D.I. 8 at Counts III-IV, Prayer for Relief ¶ 4), and pre-trial Issues of Law (D.I. 334, Ex 4, ¶¶ 71-86).

result of treating patients with Yutrepia cannot sustain UTC's burden of proof. *Brigham & Women's Hosp., Inc. v. Perrigo Co.*, 761 F. App'x 995, 1003-04 (Fed. Cir. 2019); *Genentech, Inc. v. Sandoz Inc.*, 592 F. Supp. 3d 355, 377-78 (D. Del. 2022) (An expert's "personal speculation" is insufficient to show that an infringing method would actually be practiced). INCREASE does not establish that doctors using Yutrepia will directly infringe claims 5, 6, 9 and 17.

IV. LIQUIDIA DOES NOT INDUCE INFRINGEMENT

UTC must establish that Liquidia "knowingly aided and abetted direct infringement," took "active steps to encourage, recommend, or promote infringement," and that instructions provide evidence of "intent to encourage infringement." *Lundbeck*, 87 F.4th at 1370; *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015); *Metacel Pharms. LLC v. Rubicon Research Priv. Ltd.*, No. 2023-2386, 2025 WL 1178384, at *3 (Fed. Cir. Apr. 23, 2025). Here, because there will be no direct infringement, there can be no finding of inducement. *See Takeda*, 785. F.3d at 631. Even if the Court was to find direct infringement, UTC is unable to meet its burden to show specific intent to induce infringement.

A. The Yutrepia Label Does Not Induce Infringement

The parties agree that Liquidia cannot encourage the use of Yutrepia beyond the bounds of its label. FOF178-179; UTCFOF7-8. Yutrepia is not approved for any of the measured outcomes in method claims 5, 6, 9 and 17, and measuring these outcomes is not necessary to use Yutrepia. FOF180-184. Thus, Liquidia's label does not promote, encourage or suggest using Yutrepia to achieve any of these results and does not have the specific intent to induce infringement of these claims. *Id.*; *Bayer*, 676 F.3d at 1325 (finding no inducement where FDA did not determine "that the drug is safe or effective" in causing the claimed effects); *Grünenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1339-40 (Fed. Cir. 2019) (finding no induced infringement where the label did not specifically encourage an infringing use); *Takeda*, 785 F.3d at 632. Like *Lundbeck*, the

Yutrepia label does not reference the requirements of method claims 5, 6, 9 and 17, and thus cannot induce infringement of those claims. *Lundbeck*, 87 F.4th at 1371-72. UTC's findings allege, at most, that Liquidia "knew" that doctors would infringe, without any facts establishing that Liquidia has taken "active steps" to instruct doctors to "engage in an infringing use." UTCFOF18-21 ("Liquidia knows . . ."); *see Lundbeck*, 87 F.4th at 1370. Knowledge of infringement is insufficient to establish specific intent. *Takeda*, 785 F.3d at 631.

UTC's arguments regarding Liquidia's 505(b)(2) reliance on INCREASE and literature fail to establish induced infringement. UTCFOF10. Those FDA statements are not available to "downstream users and therefore cannot cause inducement." *Metacel*, 2025 WL 1178384, at *2, 4; UTCFOF10. Further, UTC's argument amounts to "nothing more than an attempt to impose contributory infringement liability on the sale of a product knowing it will be put to infringing uses . . . ." *Lundbeck*, 87 F.4th at 1372. UTC has not asserted contributory infringement. And even if Yutrepia achieved the claimed outcomes in some patients, there is still no encouragement to infringe. *Grünenthal*, 919 F.3d at 1339-40; *Allergan*, 324 F.3d at 1324 (affirming no inducement even though the claimed effects would result because FDA had not approved drug for the claimed effects). The Yutrepia label provides certain Tyvaso results from INCREASE and none directed to claims 5, 6 and 9. Thus §14.2 does not evidence a specific intent to induce infringement of those claims. FOF185; *Vanda Pharms, Inc. v. Teva Pharms. USA, Inc.*, C.A. No. 18-651-CFC, 2022 WL 17593282, at *6-7 (FOF 50-55), *26 (D. Del. Dec. 13, 2022).

UTC points to 6MWD data in §14.2 for claim 17, asserting the "'FDA confirm[ed] that [Yutrepia] meets the clinical limitations' of claim 17." UTC Br., 8 (citation omitted). Not so, because Yutrepia is not approved to increase 6MWD. FOF178, 185. The Federal Circuit in *Bayer* held such evidence insufficient to induce infringement due to a lack of instruction because under

21 C.F.R. § 201.57(c)(2)(iv), "indications or uses '***must not be implied or suggested*** in other sections of the labeling[.]'" *Bayer*, 676 F.3d at 1322-23 (emphasis added) (citation omitted). And "merely describing an infringing mode is not the same as recommending, encouraging, or promoting, an infringing use[.]" *Takeda*, 785 F.3d at 631 (citation modified); *Lundbeck*, 87 F.4th at 1372 (that some doctors "may have been influenced by one piece of information from the label . . . does not amount to inducement."). Specific intent to induce infringement of claim 17 cannot be based on §14.2 because there is no instruction to perform the 6MWD test, nor an assertion that Yutrepia provides equivalent efficacy to Tyvaso. FOF176, 178, 185.

B. Materials Outside the Yutrepia Label Do Not Evidence Specific Intent

UTC relies on documents outside the Yutrepia label to support induced infringement. UTCFOF12; UTC Br., 5-8. But the experts agree that only the Yutrepia label is needed to safely and effectively prescribe the drug, and that the label does not direct anyone to review information regarding INCREASE, including the NEJM Paper or the Lancet Publication. FOF 186-187. These external papers are insufficient to establish Liquidia's specific intent to induce infringement.

UTC also points to "marketing materials," but failed to provide evidence that they are final versions or actually used by Liquidia now that Yutrepia is on the market. FOF 188. Many are directed to payers who do not prescribe Yutrepia (PTX384-386). To the extent they reference INCREASE, like PTX391 and PTX387, they do not state or imply Yutrepia has the same efficacy as Tyvaso in PH-ILD. FOF188; *Otsuka*, 99 F. Supp. 3d at 490 ("[C]ourts have repeatedly found incidental references to even infringing uses in [medication guides or packet inserts] insufficient to constitute instruction or encouragement, as opposed to mere permission[.]"). The rest do not mention NT-proBNP, exacerbations of ILD, FVC, statistics, or a 10m increase in 6MWD. FOF188. These marketing materials do not establish Liquidia's specific intent to induce infringement of claims 5, 6, 9 and 17.

V. THE CASE LAW UTC CITES IS INAPPOSITE

Yutrepia is not a generic of Tyvaso, and unlike the defendants in the cases cited by UTC, Liquidia made no express or implied representation that Yutrepia has equivalent efficacy to Tyvaso, nor is Yutrepia approved for the indications in the dependent claims. FOF172, 174, 176, 178; UTC Br., 5-6 (citing *Amarin Pharma, Inc. v. Hikma Pharms. USA Inc.*, 449 F. Supp. 3d 967, 1000-04 (D. Nev. 2020) (finding infringement because the ANDA label "recommends or encourages doctors to prescribe" in an infringing manner); *Allergan, Inc. v. Sandoz Inc*., No. 6:11-cv-441, 2014 WL 12622277, at *10-14 (E.D. Tex. Jan. 13, 2014) (defendants "repeatedly" indicated its ANDA product "will have the same efficacy" as the referenced product); *Bone Care Int'l, L.L.C. v. Roxane Lab'ys, Inc.*, C.A. No. 09-285-GMS, 2012 WL 2126896, at *29-32 (D. Del. June 11, 2012) (defendants' ANDA sought approval for an indication specifically covered by the asserted claim); *Intendis GMBH v. Glenmark Pharms. Ltd.*, 117 F. Supp. 3d 549, 573 (D. Del. 2015) (finding infringement under the doctrine of equivalents based on defendants' ANDA filings asserting equivalence to the reference drug)).

In *Sanofi-Aventis U.S. LLC v. Sandoz Inc.*, defendant's label demonstrated specific intent to administer with the "intentional purpose" of increasing survival, as claimed, because "overall survival" was the "major efficacy outcome." C.A. No. 20-804-RGA, 2023 WL 4175334, at *5-6 (D. Del. June 26, 2023). The outcomes are not in the Yutrepia label and none of claims 5, 6, 9 or 17 were "major" or primary outcomes–they were secondary outcomes. FOF 178; PTX147, Tbl 2.

UTC also relies on *United Therapeutics Corp. v. Liquidia Techs., Inc*., 624 F. Supp. 3d 436 (D. Del. 2022), asserting Liquidia's non-infringement argument here, was previously rejected. UTC Br., 5. Not so. The '793 patent claims only required administering a single event dose that was therapeutically effective. 624 F. Supp. 3d at 462-63; Tr., 948:17-949:12. In contrast, the claims here require specific outcomes absent from the Yutrepia label. This Court's prior

infringement decision is inapplicable to the asserted claims.

VI. DOCTOR'S KNOWLEDGE OF INCREASE IS NOT INDUCEMENT

UTC contends Liquidia induces infringement based on the known results of INCREASE. UTCFOF6, 18-21; UTC Br., 5, 9. As discussed at trial, UTC's implied inducement theory has been rejected. Tr., 951:19-953:4. Inducement requires explicit, not implicit, instructions to infringe, yet UTC argues knowledge that INCREASE demonstrated, on a "population basis," that the claimed outcomes were achieved with Tyvaso is alone sufficient. UTCFOF6. Following this logic, no company could avoid infringement, even with a label that provides no instruction to infringe, simply because doctors were aware of a prior clinical trial result. The Federal Circuit has already held that inducement does not flow from prescribing a drug "based on their background knowledge together with information in the carved-out label." *Lundbeck*, 87 F.4th at 1372; *Otsuka*, 99 F. Supp. 3d at 485 (given defendants' carve-outs, "[d]efendants cannot, as a matter of law, instruct patients and/or prescribers to use [accused products]" for the claimed method of use).

VII. UTC CONSTRUES THE CLAIMS DIFFERENTLY FOR INFRINGEMENT AND VALIDITY

Claims must be construed the same for infringement and validity and here, UTC has taken an opposite approach. *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). First, if the Court agrees with UTC's construction that the dependent claims do not require any measurement (UTC Br., 8-9), then the claims are directed only to intended results and lack patentable weight for purposes of validity. *See* Liquidia Open. Br., 1-3; FOF9-10. If, however, the Court agrees with Liquidia and the claims require measurements, then there is neither direct nor induced infringement. *See supra* §§III-IV.

Second, for infringement, UTC contends no measurements are needed, but for invalidity they require the prior art to measure and disclose that the outcomes occurred in PH-ILD patients.

FOF191. If the claims require no measurement for infringement, then no measurement is required for invalidity.

Third, Dr. Nathan applied the Court's construction of "one or more" for infringement. FOF191. For validity, he construed the claims to require "virtually all" PH-ILD patients to experience the outcomes. *Id*. If only one PH-ILD patient is needed for infringement, then only one patient needs to achieve the claimed outcome to invalidate. *See* FOF153-159.

Finally, Liquidia stipulated to infringement of claims 1 and 14 based on the Court's construction of "one or more." If, as UTC now contends, claim 1 requires "virtually all" PH-ILD patients to experience an improvement in exercise capacity, Liquidia's stipulation is void as the Court's construction has changed. *See Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 798 (Fed. Cir. 2019) (vacating and remanding judgment of noninfringement based on a stipulation which relied on erroneous claim construction). Further, if the Court adopts UTC's "virtually all" construction, then UTC has not met its burden because it is undisputed that in INCREASE, and in clinical practice, "virtually all" patients did not and will not experience an improvement in exercise capacity. FOF136. Under a "virtually all" construction, Liquidia cannot be held liable for infringement of any of claims 1, 5, 6, 9, 14 and 17. These are not issues pertaining to different burdens of proof–they are squarely UTC's differing constructions for infringement and validity.

VIII. CONCLUSION

Yutrepia does not infringe claims 5, 6, 9 and 17 and a § 271(e)(4) injunction based on these claims should be denied. If the Court finds any claims valid and infringed, Liquidia will amend its NDA to remove the PH-ILD indication rendering an injunction unnecessary. *See Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1382, 1389-91 (Fed. Cir. 2014) (affirming no § 271(e)(4)(A) injunction following finding of infringement, when defendant agreed to amend its ANDA to recite a non-infringing product); FOF172.

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Dated: July 24, 2025